

## Non-invasive patient-controlled analgesia in the management of acute postoperative pain in the hospital setting

Morlion, Bart

2018

---

Morlion , B , Schaefer , M , Betteridge , N & Kalso , E 2018 , ' Non-invasive patient-controlled analgesia in the management of acute postoperative pain in the hospital setting ' , Current Medical Research and Opinion , vol. 34 , no. 7 , pp. 1179-1186 . <https://doi.org/10.1080/03007995.2018.1462785>

---

<http://hdl.handle.net/10138/303905>

<https://doi.org/10.1080/03007995.2018.1462785>

---

unspecified

publishedVersion

---

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

! " # \$ % " & ' ) ( \* + , - ' -

(  
' ( ' ,  
(

/ 0 1, 0 / ( 2 3 4 5

6  
# # \$ % % & \$ \$ # \$  
2 ! 3 \* - . 4 2 ! 2 + / - ! 4 ( ) \$ \* + , - - . ! / 0 ) 1 ,

6 7

! ! " !  
# \$ " ! " ! % &  
' \$ ( & " ) ! "  
" \*  
+ \* , ( -

. " " / ( 0 , ! ! 1 ! ! \$ 1 !  
\*\*\* ! 1 ! " ! ( ! ) ! " 2 ! 1 ( ! 3 ) ! " , 4 (



COMMENTARY

## Non-invasive patient-controlled analgesia in the management of acute postoperative pain in the hospital setting

Bart Morlion<sup>a</sup>, Michael Schäfer<sup>b</sup>, Neil Betteridge<sup>c</sup> and Eija Kalso<sup>d</sup>

<sup>a</sup>Leuven Centre for Algology & Pain Management, University Hospitals Leuven, KU Leuven, Leuven, Belgium; <sup>b</sup>Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum, Berlin, Germany; <sup>c</sup>Neil Betteridge Associates, London, UK; <sup>d</sup>Pain Clinic, Departments of Anaesthesiology, Intensive Care, and Pain Medicine, Helsinki University Central Hospital, Helsinki, Finland

### ABSTRACT

**Objective:** Acute postoperative pain is experienced by the majority of hospitalized patients undergoing surgical procedures, with many reporting inadequate pain relief and/or high levels of dissatisfaction with their pain management. Patient-controlled analgesia (PCA) ensures patient involvement in acute pain control, a key component for implementing a quality management system. This narrative article overviews the clinical evidence for conventional PCA and briefly discusses new, non-invasive PCA systems, namely the sufentanil sublingual tablet system (SSTS) and the fentanyl iontophoretic transdermal system (FITS).

**Methods:** A Medline literature search (“patient-controlled analgesia” and “acute postoperative pain”) was conducted to 1 April 2017; results from the main clinical trials are discussed. Additional literature was identified from the reference lists of cited publications.

**Results:** Moderate to low quality evidence supports opioid-based intravenous PCA as an efficacious alternative to non-patient-controlled systemic analgesia for postoperative pain. However, despite the benefits of PCA, conventional intravenous PCA is limited by system-, drug- and human-related issues. The non-invasive SSTS and FITS have demonstrated good efficacy and safety in placebo- and intravenous morphine PCA-controlled trials, and are associated with high patient/healthcare practitioner satisfaction/ease of care ratings and offer early patient mobilization.

**Conclusions:** Evidence-based guidelines for acute postoperative pain management support the use of multimodal regimens in many situations. As effective and safe alternatives to conventional PCA, and with the added benefits of being non-invasive, easy to use and allowing early patient mobilization, the newer PCA systems may complement multimodal approaches, or potentially replace certain regimens, in hospitalized patients with acute postoperative pain.

### ARTICLE HISTORY

Received 19 December 2017  
Revised 22 February 2018  
Accepted 8 March 2018

### KEYWORDS

Acute postoperative pain;  
fentanyl iontophoretic  
transdermal system;  
morphine; patient-  
controlled analgesia;  
sufentanil sublingual  
tablet system

## Introduction

The majority of patients who undergo surgical procedures experience acute postoperative pain, but evidence suggests that less than half report adequate postoperative pain relief<sup>1,2</sup>. Moreover, many patients report a high level of dissatisfaction with their pain management<sup>3–5</sup>. Numerous recent and ongoing initiatives at the national and international level, including the 2001–2011 US congress-initiated “Decade of Pain Control and Research”<sup>6</sup>, and the joint 2017 International Association for the Study of Pain (IASP)/European Pain Federation (EFIC) “Global/European Year Against Pain After Surgery”<sup>7</sup>, have increased awareness among key stakeholders. In addition, studies have shown that the introduction of acute pain services and/or acute pain management programs can be associated with improved acute postoperative pain management, and good pain control has become an indicator of quality of care and good clinical practice<sup>8–12</sup>. Nevertheless, although adequate

treatment of acute postoperative pain can improve patient quality of life and satisfaction with care, as well as enhance clinical resource management and reduce long-term costs of care, acute pain remains undertreated and its management is suboptimal<sup>13</sup>.

There are numerous short- and long-term consequences of inadequately treated acute pain, including hyperglycemia, insulin resistance, an increased risk of infection, decreased patient comfort and satisfaction and the chronification of pain<sup>13–16</sup>. The processes responsible for the transition from acute postoperative or post-traumatic pain to pathological chronic pain are complex and poorly understood<sup>15,17,18</sup>. Biological, psychological and social/environmental factors, and known polymorphisms in human genes, are all involved in perpetuating the pain<sup>18</sup>.

Valid, reliable and active assessment of pain in the postoperative phase is an important factor in achieving improved postoperative pain organization and management in hospitals<sup>19,20</sup>. A study using repeated annual audits over a 3 year

period in the general surgery and orthopedic departments of a large university hospital setting led to the introduction of mandatory training in postoperative pain management for all key stakeholders, upgraded care guidelines/protocols and regular staff meetings<sup>20</sup>. During the 3 year period, the assessment of pain according to protocols increased from 71% to 91% in the surgical wards and from 60% to 88% in the orthopedic wards<sup>20</sup>.

Persistent acute postoperative pain can be prevented using a variety of multidisciplinary team approaches (e.g. physician-led, nurse-led, pharmacist-led and/or patient-controlled), including multimodal pharmacological strategies, psychological strategies, modified surgical techniques, procedure-specific postoperative pain management and enhanced postoperative recovery programs<sup>21–25</sup>.

Indeed, many preoperative, intraoperative and postoperative interventions and management strategies are available for reducing and managing postoperative pain. Interestingly, in a large survey involving >16,000 surgical patients from 17 countries “correlates of satisfaction” with pain treatment were evaluated<sup>26</sup>. Three items showed strong association with overall satisfaction: (1) more pain relief; (2) greater participation in decisions regarding treatment; (3) no desire to have received more treatment. The authors concluded that while the patients’ satisfaction with postoperative pain treatment was associated with their actual pain experience, it was more strongly influenced by their impressions of improvement and appropriateness of care<sup>26</sup>.

Patient involvement in pain control is a key component for the implementation of a quality management system in the surgical setting<sup>25,27,28</sup>. A rational extension of this goal is allowing patients to control an on-demand system which permits them to manage their own pain relief<sup>29</sup>.

## Patient-controlled analgesia: background

One of the founding pioneers of patient-controlled analgesia (PCA), Dr. Philip H. Sechzer, maintained that “if patients had more control of their medication, their anxiety and pain would be less severe, and they would dose themselves with less medication”<sup>30</sup>. Dr. Sechzer originally introduced “patient-controlled analgesic demand systems” into medical practice in the 1960s<sup>31,32</sup>.

PCA enables the patient to self-administer predetermined doses of an analgesic when they deem it necessary. The specific doses are programmed by a trained healthcare professional, and the device is also programmed to limit the administration of each dose or a cumulative amount of drug over a specific time interval. The technique has progressed over recent decades and sophisticated microprocessor-controlled infusion pumps are currently used to deliver the required doses of analgesic<sup>33</sup>. PCA typically involves intravenous (IV) opioid delivery, generally using morphine, but may include other drugs (such as NSAIDs or local anesthetics) or other routes of administration (for example, epidural, subcutaneous, transdermal or nasal administration)<sup>33</sup>. Indeed, PCA represents a conceptual framework for the administration of analgesics. PCA is commonly used for acute

postoperative pain, but it can also be used for the management of other types of acute pain such as in the hospital emergency department<sup>33</sup>. It has been documented that acute pain is not controlled adequately in the emergency care setting<sup>34,35</sup>. This observation of suboptimal pain management may extend to situations in which the patient requires transfer between hospitals (usually for a higher level of care) in emergency vehicles<sup>36,37</sup>. In some jurisdictions, ambulances are staffed by paramedics with basic life support training; doctors and nurses are not available to administer analgesics. Therefore, although there is currently insufficient clinical evidence or guidelines regarding the use of PCA for patients with acute injury during transfer to a higher level of care<sup>38</sup>, there is a potential role for PCA to provide sufficient acute pain management in this setting.

The aim of this commentary is to provide an overview of the clinical effectiveness and safety of, and patient satisfaction with, conventional PCA for acute postoperative pain in the hospital setting, and briefly discuss new, non-invasive PCA systems, namely the sufentanil sublingual tablet system (SSTS; Zalviso<sup>1</sup>) and the fentanyl iontophoretic transdermal system (FITS; Ionsys<sup>2</sup>), in this clinical setting.

## Methods

This commentary is based largely on recently published best clinical evidence<sup>27,39,40</sup>, supplemented with new literature published since those publications (in 2015) and data from current clinical practice guidelines for the management of postoperative pain. Therefore, a literature search was conducted in the Medline database using the terms “patient-controlled analgesia” and “acute postoperative pain” from 1 January 2015 to 1 April 2017 (113 records) and results from the main clinical trials, published in English, are discussed. Additional literature was identified from the reference lists of cited publications.

## Overview of patient-controlled analgesia

This section provides an overview of the clinical evidence regarding PCA, based largely on a recently published Cochrane systematic review<sup>40</sup> and clinical evidence evaluated with scientific rigor by the Australia and New Zealand College of Anaesthetists (ANZCA) and Faculty of Pain Medicine (FPM)<sup>39</sup>.

The recent Cochrane review of 49 randomized, controlled trials ( $n = 3412$ ) showed that there is moderate to low quality evidence that opioid-based IV PCA is an efficacious alternative to non-patient-controlled systemic analgesia for postoperative pain control<sup>40</sup>. For the primary outcome, participants receiving IV PCA had lower visual analog scale (VAS) pain intensity scores versus non-PCA over most time intervals. For example, VAS scores over 0 to 24 hours were 9 points lower (95% confidence interval [CI]  $-13$  to  $-5$ ; moderate quality evidence) and over 0 to 48 hours were 10 points lower (95% CI  $-12$  to  $-7$ ; low quality evidence). Among the evaluated secondary outcomes, participants were more satisfied with PCA (81% versus 61%,  $p = .002$ ) and consumed higher amounts of

opioids than non-PCA recipients (0 to 24 hours, 7 mg more of intravenous morphine equivalents, 95% CI 1 mg to 13 mg)<sup>40</sup>. With regard to safety, individuals receiving PCA had a higher incidence of pruritus (15% versus 8%,  $p = .01$ ) but had a similar incidence of other adverse events. In addition, there was no overall between-group difference in the length of hospital stay<sup>40</sup>.

A pooled analysis of data from 165 studies in approximately 20,000 patients showed that patients who received intramuscular (IM) opioid analgesia were approximately two- to three-fold more likely to experience moderate-to-severe (67.2% vs. 35.8%) or severe (29.1% vs. 10.4%) acute postoperative pain compared with individuals who received IV PCA<sup>41</sup>.

The largest randomized, controlled study compared the efficacy and safety of IV PCA versus IM analgesia in 328 patients after major abdominal surgery (cholecystectomy: 105 patients; hysterectomy: 223 patients)<sup>42</sup>. Patients receiving PCA required less total analgesia (cholecystectomy: 663 mg vs. 809 mg; hysterectomy: 696 mg vs. 1027 mg), had a shorter length of hospital stay (cholecystectomy: 4.5 days vs. 6.3 days; hysterectomy: 4.5 days vs. 4.8 days) and lower average total costs (drugs, nursing and pharmacy time: US\$13.43 vs. US\$41.33) than patients receiving IM analgesia. No complications attributable to the route of administration were reported<sup>42</sup>.

Taken together, these findings highlight the overall importance and benefits of PCA versus conventional non-PCA approaches. Indeed, based on the clinical evidence discussed above, current pain management guidelines support the use of PCA for postoperative pain management. For example, recently published clinical practice guidelines from the American Pain Society, with input from the American Society of Anesthesiologists, recommend that IV PCA be used for postoperative systemic analgesia when the parenteral route is needed (strong recommendation, moderate-quality evidence)<sup>25</sup>. These recommendations for the use of PCA are also supported in other management and clinical practice guidelines<sup>43</sup>. German guidelines<sup>44,45</sup> note that meta-analyses show that IV PCA systems achieve better analgesia compared with conventional IM, subcutaneous (SC) and IV regimens<sup>46,47</sup>, and are preferred by patients<sup>48</sup>. Furthermore, the German guidelines note that controlled IV analgesia applied by nurses can be comparable to that achieved with IV PCA, but only if it is carried out systematically and continuously<sup>49</sup>. Given that the fundamental difference between the two treatment groups in the latter study is the avoidance of nurses having to repeatedly attend to and supervise the patient to assess pain relief and administer analgesia, the findings imply that a more resource-intensive approach may be required with controlled IV analgesia than with IV PCA to achieve similar levels of analgesia<sup>49</sup>.

Despite the benefits of PCA, conventional approaches are associated with some drawbacks. One of the limitations of IV PCA is the large degree of variability in the parameters used in clinical studies (e.g. bolus doses, lockout intervals and maximum permitted cumulative doses), leading to uncertainty about the optimal PCA program and possibly restricting the flexibility, and efficacy, of the technique. Moreover, in

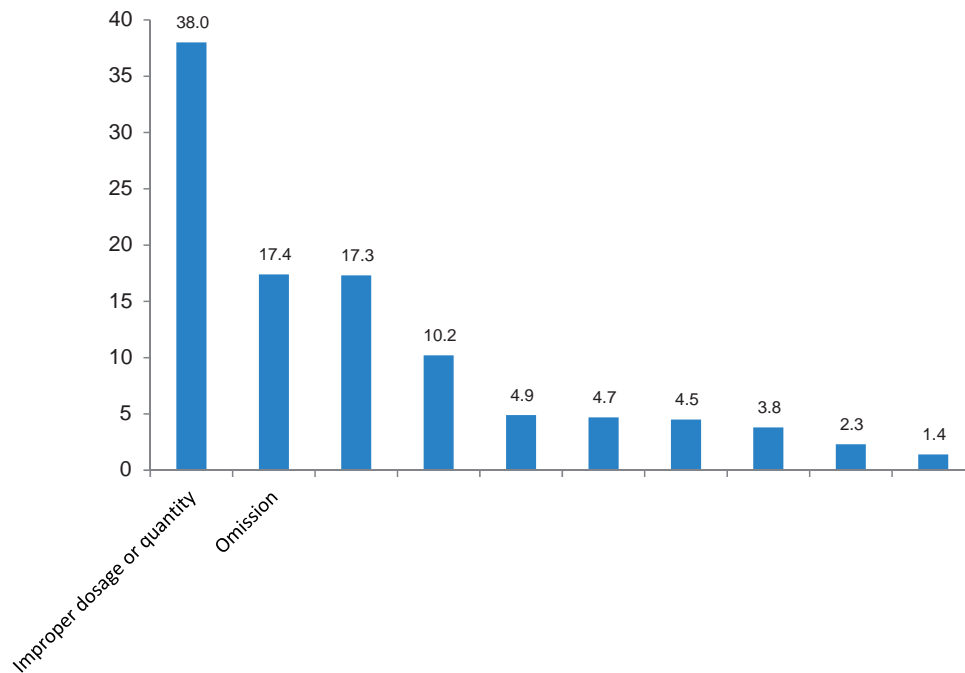
order for patients to receive maximum benefit from IV PCA, individual prescriptions may need to be adjusted<sup>50</sup>.

Data from a prospective, multicenter, observational study showed that IV PCA in acute postoperative pain management is labor intensive and involves numerous time-consuming tasks, oversight of IV PCA and ongoing staff training<sup>51</sup>.

Other potential drawbacks to conventional IV PCA result from the complex technology required, including the need for a patent IV line and tethering of the patient to an IV PCA pump mounted on an IV pole which can result in infection, reduced mobility and analgesic gaps as a consequence of IV catheter infiltration or IV tubing obstruction<sup>52,53</sup>. In addition, IV PCA is prone to human dosing errors due to the use of a programmable pump, many of which cause harm to patients and add a significant cost burden to healthcare systems<sup>54,55</sup>. A 5 year retrospective analysis (2000–2004) of a US voluntary medication error-reporting database showed that 1% (9571/919,241) of all reported errors were PCA-related and, of these, 38% involved an improper dosage or quantity, while 17.4% involved an omission and 17.3% an unauthorized or wrong drug (Figure 1). Human factors were identified as the main cause of PCA errors, with equipment issues (19.5%) and similar drug names and product packaging (11.6%) also implicated. The most common factors which contributed to PCA-associated errors were distractions (37.8%) and inexperienced staff (26.3%)<sup>54</sup>. Drugs most frequently associated with PCA errors were morphine (49.2%), hydromorphone (21.6%), meperidine (11.8%), fentanyl (4.6%) and naloxone (0.9%)<sup>54</sup>. Programming errors were also identified as the largest contributory factor to critical incidents with conventional PCA systems in a 5 year analysis (2002–2006) of data from an Irish university hospital setting<sup>56</sup>.

Factors associated with IV PCA have resulted in relatively low uptake of this treatment modality, despite it being included in many guidelines<sup>52,53,55,57,58</sup>. Indeed, the proportion of postoperative patients receiving IV PCA remains relatively small despite the fact that, as discussed earlier, clinical practice guidelines recommend PCA in preference to conventional routes of administration; national surveys recorded 21.4% use of IV PCA in France<sup>59</sup> and only 5% in Italy<sup>60</sup>.

Patient characteristics can also influence the use of conventional PCA. A study in 100 patients who used only morphine PCA for the first 24 hours after upper abdominal surgery showed that male patients ( $n = 46$ ) required significantly more morphine than female patients ( $n = 54$ ) to achieve similar levels of pain relief ( $p < .05$ )<sup>61</sup>. There was an inverse correlation between age and morphine consumption in both males ( $r = -0.684$ ,  $p < .00005$ ) and females ( $r = -0.502$ ,  $p < .00005$ ). No correlation was found between morphine consumption and patient weight. The pattern of hourly morphine consumption appeared to follow a diurnal rhythm, with peak times of demand at 0900 and 2000 hours<sup>61</sup>. An inverse correlation between patient age and morphine consumption was also observed in a large ( $n = 1308$ ) retrospective analysis of patients using postoperative IV PCA over 3 days<sup>62</sup>. For all operations, weight, age, procedures involving malignant disease and surgical sites were significantly associated with total morphine consumption<sup>62</sup>. Individual patient psychological factors can also play a



role in the success or failure of using PCA; for example, and decreases the most common issues associated with conventional PCA systems. Moreover, the SSTS is able to display a demand to be assessed.<sup>63</sup>

Whilst recognizing the underlying value and importance of PCA and acknowledging the potential drawbacks of conventional approaches to PCA, more recent clinical research has focused on developing improved PCA systems. Consequently, alternative noninvasive routes of administration have been evaluated, with the aim of simplifying the process and avoiding errors; for example, noninvasive sublingual and transdermal routes of PCA have been shown to be both safe and effective compared with conventional intravenous PCA. The following sections provide a brief overview of recently introduced innovative needle-free PCA systems, focusing specifically on the SSTS and the FITS.

The efficacy and safety of the SSTS have been demonstrated in several phase II and phase III double-blind, randomized, comparative clinical studies, conducted in patients undergoing major open abdominal or orthopedic surgery.<sup>65-68</sup>

In placebo-controlled studies, the SSTS was significantly better than placebo with regard to the primary endpoint (summed pain intensity difference [SPID] 48;  $p < .001$ ).<sup>65,67</sup> SPID and total pain relief (TOTPAR) scores were significantly higher with the SSTS than with placebo from early time points through to 72 hours.<sup>65,67</sup> In a phase III active-comparator trial, the SSTS was associated with a more rapid onset of analgesia (statistically significantly greater pain control at 1, 2, and 4 hours; all  $p < .01$  compared with IV morphine PCA), and higher success rates, based on patient global assessment (PGA) and investigator global assessment (IGA) of the method of pain control over 24, 48 and 72 hours.<sup>66</sup>

### Sufentanil sublingual tablet system

The sufentanil sublingual tablet system (SSTS) is a pre-programmed, non-invasive, handheld device which dispenses a single sufentanil bioadhesive nanotablet (3 mm in diameter, 0.75 mm thickness; 15g), with a minimum 20 minute inter-dose lockout period.<sup>63</sup> The dispenser can be used by the same patient over the course of 3 days of treatment; prefilled cartridges contain 40 tablets (providing about a 2 day supply) and cartridges are discarded after patient use. Sufentanil nanotablets dissolve promptly when administered sublingually.<sup>64</sup> The pre-programmed device uses a radiofrequency identification thumb tag, which allows self-administration only by the assigned patient (healthcare providers or patient relatives cannot administer the drug); this aspect of the SSTS

Indeed, 78.5% and 65.6% of patients achieved success 'excellent' or 'good' on the PGA over 48 hours (primary endpoint) in the SSTS and IV morphine PCA groups, respectively, demonstrating non-inferiority as well as statistical superiority in favor of the SSTS group ( $p < .007$ ). Moreover, non-inferior pain relief was sustained over a 48-hour period with the SSTS compared with IV morphine PCA. Patient and nurse ease of care (EOC) and satisfaction scores were significantly higher in patients using the SSTS than in those using IV morphine PCA; patients in the SSTS group reported significantly better patient mobility ("ease of movement") than IV morphine PCA recipients ( $p < .001$ ).<sup>66</sup>









